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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/863,693	ARATHOON ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20030925*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed September 25, 2003 is acknowledged and has been entered. Claims 1, 8, 9, 11, 19, and 20 have been canceled. Claims 33, 36, 41, and 43 have been amended. Claims 45-51 have been added.

2. Claims 30-51 are pending in this application and are currently under prosecution.

Information Disclosure Statement

3. The information disclosure filed September 25, 2003 has been considered. An initialed copy is attached hereto.

Response to Amendment

4. Regarding the rejections of claims 1, 8, 9, 11, 19, 20, 33-38, and 41-44 under 35 U.S.C. 103(a) as being unpatentable over Mallender et al., as evidenced by Gulliver et al., in view of U.S. Patent Nos. 5,731,168-A, 5,807,706-A, and 5,821,333-A, of claims 1, 8, 9, 11, 19, 20, and 30-44 under 35 U.S.C. 103(a) as being unpatentable over Vaughan et al. in view of Bruynck et al. or Vuillez et al. and in view further view of U.S. Patent Nos. 5,731,168-A, 5,807,706-A, and 5,821,333-A, and of claims 1, 8, 9, 11, 19, 20, and 30-44 under 35 U.S.C. 103(a) as being unpatentable over Vaughan et al. in view of Reddy et al. and in view further view of U.S. Patent Nos. 5,731,168-A, 5,807,706-A, and 5,821,333-A, which were set forth in sections 6, 7, and 8 of the Office action mailed March 27, 2003: At page 11 (paragraph 3) of the amendment filed September 25, 2003, Applicant has stated the subject matter disclosed and claimed by U.S. Patent Nos. 5,731,168-A, 5,807,706-A, and 5,821,333-A were owned by the same person or subject to an obligation of assignment to the same person at the time the instantly claimed invention was made. Accordingly, Applicant makes a clear statement of entitlement to exclude U.S. Patent Nos.

5,731,168-A, 5,807,706-A, and 5,821,333-A as prior art, as provided by 35 USC § 103(c).

Response to Arguments

5. Applicant's arguments set forth in the amendment filed September 25, 2003 with respect the grounds of rejection in the previous Office action mailed March 27, 2003 have been considered but are moot in view of the new grounds of rejection.

Grounds of Claim Rejections Withdrawn

6. The grounds of rejection set forth in the previous Office action mailed March 27, 2003 have been withdrawn because the rejected claims were canceled by the amendment filed September 25, 2003 or, as explained above, U.S. Patent Nos. 5,731,168-A, 5,807,706-A, and 5,821,333-A have been disqualified by Applicant's amendment in accordance with the provision under 35 USC § 103(c) as prior art under § 103(a). Nevertheless, with regard to the grounds of rejection set forth under 35 USC §103(a) in view of Mallendar et al., although Gulliver et al. teaches the light chain variable domains of the bispecific antibody of Mallendar et al. are nearly identical, the prior art is silent as to whether the only differences in the amino acid sequences of the two light chain variable domains reside outside the CDRs.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 33-38, 41-47, and 49-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a new matter rejection.

Claims 33, 36, 41, 43, and 47 recite "at least 98%", whereas claim 46 recites "at least about 98%". At page 9 of the amendment filed Sept 25, 2003, Applicant has submitted written support for the claim language can be found in the specification at page 11, line 16, through page 14, line 18, at page 22, lines 17-24, page 56, lines 13-29, and page 97, line 10, through page 98, line 4. However, while the disclosure at page 97 would provide written support for "98%", it does not provide proper and sufficient written support for "at least 98%" or "at least about 98%".

Claim 45 recites "an original antibody variable light chain of the first and second polypeptide". Although, again, Applicant has submitted written support for the claim language can be found in the specification, the specification, including the claims, as originally filed, does not appear to describe "an original antibody variable light chain of the first and second polypeptide".

These issue might be resolved if Applicant were to point to particular disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary written support.

Otherwise, regarding to the latter issue, as a suggestion, Applicant can obviate this ground of rejection by amending claim 45 to recite the language that used in the specification at page 13, lines 17-21.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claim 47 is rejected under 35 U.S.C. 102(b) as being anticipated by Mallender et al. (*Journal of Biological Chemistry* **269**: 199-206, 1994; of record), as evidenced by Gulliver et al. (*Journal of Biological Chemistry* **269**: 7934-7940, 1994; of record).

Given the broadest reasonable interpretation, claim 47 encompasses a method for making a bispecific antibody, wherein said method comprises selecting a variable light chain domain that has at least 98% sequence identity to each variable light chain of a first and second antibody, wherein the first and second antibodies bind different antigens.

As evidenced by Gulliver et al., the variable light chains of SCA 4-4-20 and SCA 04-01 are "nearly identical" (abstract). As evidenced by Applicant's remark at page 12, paragraph 2, of the amendment filed September 25, 2003: nearly identical light chains have at least 98% identity. Accordingly, the variable light chains of SCA 4-4-20 and SCA 04-01 are deemed to have at least 98% identity.

Mallendar et al. teaches a method for preparing a bispecific antibody; see entire document, particularly the abstract. Malendar et al. discloses selecting the variable light chains of a first and second antibody, wherein the first and second antibody, namely SCA 4-4-20 and SCA 04-01 bind different antigens, namely fluorescein and single-stranded DNA, respectively (abstract). Malendar et al. teaches culturing a host cell comprising a nucleic acid sequence encoding a first variable heavy chain domain from the first antibody, a second nucleic acid sequence encoding a second variable heavy domain from the second antibody, a third nucleic acid sequence encoding a selected variable light chain domain, and a fourth nucleic acid sequence encoding the other selected variable light chain domain; see, e.g., page 200, column 2. Malendar et al. teaches recovering the bispecific antibody from the cell culture; see, e.g., page 200, column 2.

The specification discloses that "a multimerization domain" is "a region of each of the polypeptides of the heteromultimer", which "promotes the stable interaction of the chimeric molecules within the heteromulitmer complex" and/or

which "promotes interaction between a specific first polypeptide and a specific second polypeptide" (page 19, line 27, to page 20, line 2). Furthermore, the specification discloses: "The multimerization domains may interact via an immunoglobulin sequence, leucine zipper, a hydrophobic region, a hydrophilic region, or a free thiol which forms an intermolecular disulfide bond between the chimeric molecules of the chimeric heteromultimer" (page 20, lines 5-9). Notably, the specification does not exclude multimerization domains that interact via a covalent, or more particularly a peptide bond. Both the first and second nucleic acid sequences encoding the portions the bispecific antibody of Mallendar et al. encode a "multimerization domain", which "interact to form a bispecific antibody".

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 30-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reddy et al. (*Anticancer Research* **13**: 2077-2083, 1993; of record), Vaughan et al. (*Nature Biotechnology* **14**: 309-314, 1996; of record), and Zhu et al. (*Protein Science* **6**: 781-788, 1997).

Reddy et al. teaches a method for preparing a bispecific antibody for cancer therapy that comprises binding specificity for the tumor-associated antigen CEA and an anticancer agent, namely doxorubicin.

Vaughan et al. teaches a human antibody fragment with sub-nanomolar affinity that binds doxorubicin, namely VoDox-1; see entire document, particularly page 313, Table 3. and CEA. Vaughan et al. discloses VoDox-1 was identified as having the highest affinity constant of the antibodies produced (page 311, column 1). Vaughan et al. teaches VoDox-1 comprises a light chain variable domain (V_L) identified as "L12a" (page 312, Table 2).

In addition, Vaughan et al. teaches a human antibody fragment with sub-nanomolar affinity that binds CEA, namely CEA-6 (page 313, Table 3, in particular). Vaughan et al. teaches CEA-6 was tested in flow cytometry with CEA+ HeLa cells and is shown to recognize CEA in the context of a cell surface, binding strongly and specifically (page 311, column 1). Vaughan et al. teaches CEA-6 has been used to immunolocalize CEA in tissue sections (page 312, column 2). Vaughan et al. discloses CEA-6 has a binding affinity of 7.7 nM (page 313, Table 3), which Vaughan et al. teaches compares favorably with CEA antibodies derived from rodent immunization (page 312, column 2). Vaughan et al. teaches the very high binding affinity of the antibody enables its direct use in a variety of bioassays (page 312, column 1). Furthermore, Vaughan et al. teaches slow off-rates are an important characteristic for antibodies used for human therapy (page 312, column 2). Vaughan et al. discloses CEA-6 has an off-rate of 6.2×10^{-3} s^{-1} (page 313, Tables 3 and 4). Vaughan et al. discloses that the best antibodies previously isolated from a large synthetic repertoire of Fab fragments were of high affinity but had relatively fast off-rates, whereas the antibodies derived from their library have a slower off-rate than either those from rodent immune responses or scFvs from smaller libraries (page 312, column 2). Vaughan et al. teaches CEA-6 comprises a light chain variable domain (V_L) identified as "L12a" (page 312, Table 2).

Furthermore, Vaughan et al. teaches the main focus of investigators is to generate human antibodies for therapy, as it was well known that human antibodies provide numerous advantages over rodent antibodies (page 309, column 1). Vaughan et al. discloses their work indicates that neither immunization nor affinity maturation is a prerequisite for generating high affinity antibodies and the relative speed and ease with which antibodies with high affinities can be isolated from the scFv repertoire suggests conventional hybridoma technology may be superceded by large phage libraries in the production of high affinity human monoclonal antibodies (page 313, column 1).

Zhu et al. teaches methods for producing bispecific antibodies; see entire document. Moreover, Zhu et al. compares two engineering strategies for producing bispecific antibodies, each of which enhance the formation of functional bispecific antibodies; see, e.g., page 785, column 1. Zhu et al. teaches the strengths, as well as the limitations associated with both approaches (page 785, column 2). The first approach involves the installation of non-naturally occurring cysteine residues, which form antibody-stabilizing disulfide bonds; see, e.g., the abstract. Zhu et al. teaches this first approach eliminates the undesirable production of higher order aggregates and mulitmers and increases the immunoreactive fraction, as compared to the conventional approach that does not involve engineering additional disulfide bonds (page 785, column 2). Zhu et al. teaches an additional attractive feature of the engineered disulfide-stabilized antibody is that it can be distinguished from other species by SDS-PAGE (page 785, column 2). Zhu et al. teaches the major drawback of this first approach is the very low yield of soluble protein, but also Zhu et al. discloses engineering a disulfide bond across the C_H3 domain interface of an antibody can facilitate heterodimerization without compromising expression titers form human embryonic kidney cells (page 785, column 2). Even so, Zhu et al. discloses the fraction of recovered disulfide-stabilized antibody that was functional following expression in *E. coli* was improved, as compared to the fraction of recovered diabody produced by the conventional methodology (abstract). The second strategy used by Zhu et al. is the so-called "knobs-into-holes" engineering approach, which involves making sterically complementary mutations to install a protuberance and a corresponding cavity by; see, e.g., page 785, column 1. Zhu et al. teaches amino acid replacements at either interface to create a protuberance and a complementary cavity are sufficient to improve the fraction of functional bispecific antibody, while maintaining overall recoverable yields and affinity for the antigens close to that of the antibody produced by the conventional methodology (abstract).

It would have been *prima facie* obvious to one ordinarily skilled in the art to produce a high-affinity human bispecific antibody having dual binding specificity for doxorubicin and CEA using the methodology taught by Zhu et al. and the scFv antibodies CEA-6 and VoDox-1 of Vaughan et al., because Reddy et al. teaches a therapeutically useful bispecific antibody having such dual binding specificity, but which is a rodent antibody, whereas Vaughan et al. teaches a human scFv antibody having high affinity, and a slow off-rate, with the specificity of one arm or the other of the antibody of Reddy et al., and Zhu et al. teaches methods for producing a bispecific antibody from the scFv antibodies of Vaughan et al., which results in products having relatively increased stability and relatively higher yields, as compared to bispecific antibodies produced by other more conventional methodology. One ordinarily skilled in the art would have been motivated at the time the invention was made to do so because the bispecific antibody can be used in accordance with the teachings of Reddy et al. to target doxorubicin to CEA+ cancer cells in a subject.

Conclusion

13. No claims are allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will

the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Christina Chan can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
June 11, 2004

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